The role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer: A systematic review

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BACKGROUND: Cholangiocarcinoma and gallbladder cancer are difficult to treat curatively. The treatment of choice is surgery, dependent on detection at a resectable stage. No chemotherapy or radiotherapy options have shown substantial activity. Gemcitabine has demonstrated response in similar cancers. Considering the lack of treatment options for cholangiocarcinoma and gallbladder cancer, a systematic review of the evidence on gemcitabine use for these indications was performed.
OBJECTIVE: To perform a systematic review to evaluate the role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer.
METHODS: The MEDLINE database was searched (1996 to March 2005) using the medical subject headings 'gemcitabine' and 'gallbladder neoplasms' with results limited to English only. Proceedings from the 1998 to 2004 meetings of the American Society of Clinical Oncology, including the 2004 Gastrointestinal Cancers Symposium, were searched for relevant abstracts. The Canadian Medical Association infobase and the National Guidelines Clearinghouse were also searched for practice guideline reports. Reports were selected and reviewed by two reviewers, and the reference lists from those were searched for additional trials.
RESULTS: A total of 13 single-arm phase II trial reports were obtained.
CONCLUSIONS: In appropriate patients with gallbladder cancer or cholangiocarcinoma, surgery offers the best chance for survival and should remain the first treatment of choice. For patients not considered candidates for surgery, but willing and able to tolerate chemotherapy alone or in combination with a fluoropyrimidine (such as 5-fluorouracil or capecitabine), gemcitabine appears to be a reasonable alternative to best supportive care, although this conclusion has not been confirmed with a randomized controlled trial.

Key Words: *Cholangiocarcinoma; Gallbladder cancer; Gemcitabine; Systematic review*

Le rôle de la gemcitabine dans le traitement du cholangiocarcinome et du cancer de la vésicule biliaire : Un examen systématique

HISTORIQUE : Le cholangiocarcinome et le cancer de la vésicule biliaire sont difficiles à guérir. Le traitement de choix demeure la chirurgie, si la maladie est décelée à une étape où la résection est possible. Aucun traitement chimiothérapeutique ou radiothérapeutique ne s'est révélé très actif. La gemcitabine a provoqué des réponses dans des cancers similaires. Étant donné l'absence de possibilités de traitement du cholangiocarcinome et du cancer de la vésicule biliaire, un examen systématique de l'utilité probante de la gemcitabine pour ces indications a été effectué.
OBJECTIFS : Procéder à un examen systématique pour évaluer le rôle de la gemcitabine dans le traitement du cholangiocarcinome et du cancer de la vésicule biliaire.
MÉTHODOLOGIE : La base de données MEDLINE a fait l'objet d'une recherche (1996 à mars 2005) à l'aide des termes « *gemcitabine* » et « *gallbladder neoplasms* », les résultats étant limités à l'anglais. Des recherches ont été menées dans les comptes rendus des congrès de 1998 à 2004 de l'*American Society of Clinical Oncology*, y compris le symposium 2004 des cancers gastro-intestinaux, afin de trouver des résumés pertinents. Les bases de données de l'Association médicale canadienne et de la *National Guidelines Clearinghouse* ont également fait l'objet de recherches afin de trouver des guides de pratique clinique. Les rapports ont été sélectionnés et analysés par deux réviseurs, et leurs listes de référence ont aussi fait l'objet de recherches afin de trouver des essais supplémentaires.
RÉSULTATS : Au total, 13 rapports d'essais de phase II à une branche ont été obtenus.
CONCLUSIONS : Chez les patients pertinents atteints d'un cancer de la vésicule biliaire ou d'un cholangiocarcinome, la chirurgie offre la meilleure chance de survie et devrait demeurer le traitement de choix. Pour les patients qui ne peuvent être candidats à une opération mais qui sont prêts à tolérer une chimiothérapie seule ou en association avec de la fluoropyrimidine (comme du 5-fluorouracil ou de la capécitabine) et en mesure de la faire, la gemcitabine semble constituer une solution raisonnable aux meilleurs soins de soutien, même si cette conclusion n'a pas été étayée par un essai aléatoire et contrôlé.

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Cancers of the biliary tree, including cholangiocarcinoma and gallbladder cancer, are difficult to treat with curative intent for several reasons. First, they are rare in the population (1), making adequate accrual into randomized controlled trials (RCTs) difficult and time-consuming; second, many patients present with unresectable disease and are eligible for palliative treatment only (1); and third, no chemotherapy or radiotherapy options tested to date have shown any substantial activity (1). Currently, the treatment of choice for these cancers is surgery, but surgery is dependent on the cancer being detected at an early, resectable stage. Recently, the role of radiation therapy in combination with chemical radiosensitizers has been investigated (1).

In Canada, gallbladder cancer represented 0.28% (381 of 134,413) of all new cancers in 2000 and 0.41% (259 of 62,672) of all cancer deaths (2). Gallbladder cancer affected female patients at 2.3 times the rate for male patients for both incidence and mortality (2). Incidence, mortality and sex-specific data were not available for cholangiocarcinoma.

Gemcitabine is a newer drug available to Ontario clinicians. It has demonstrated a treatment response in pancreatic cancer patients (3,4) and is also indicated for the treatment of non-small cell lung cancer (4). Gemcitabine is an intravenous drug that is metabolized within tumour cells by nucleoside kinases to the active gemcitabine diphosphate and gemcitabine triphosphate nucleosides. These gemcitabine nucleosides inhibit DNA synthesis via two processes. In the first, gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing reactions that generate the deoxynucleoside triphosphates for DNA synthesis. In the second, gemcitabine triphosphate competes with deoxycytidine 5′-triphosphate for incorporation into DNA. By using these two mechanisms, gemcitabine induces a programmed cell death response by blocking the progression of dividing cells through the G1/S phase boundary (4).

Considering the demonstrated treatment response of gemcitabine in similar cancers, the lack of effective alternative treatment options for cholangiocarcinoma and gallbladder cancer, and the interest by some Ontario clinicians to have access to this drug, the Gastrointestinal Cancer Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) decided to conduct a systematic review of the evidence to answer the following clinical question: what is the role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer? The outcomes of interest included overall response rates and survival, adverse effects and quality of life. This systematic review served as the basis for a clinical practice guideline.

METHODS

The present report, produced by the PEBC's gastrointestinal cancer DSG, is a convenient and up-to-date source of the best available evidence on the role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer developed through a systematic review of the available evidence. Members of the DSG disclosed any potential conflicts of interest. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature search strategy

The MEDLINE database was searched from 1996 to the second week of March, 2005. The medical subject headings 'gemcitabine' and 'gallbladder neoplasms' were combined and results were limited to English only. In addition, conference proceedings from the 1998 to 2004 meetings of the American Society of Clinical Oncology were searched for abstracts of relevant trials, including the 2004 Gastrointestinal Cancers Symposium abstracts. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines. An additional article not found in the literature search, because it was too recent to be indexed, was obtained from a Gastrointestinal Cancer DSG member.

Relevant articles and abstracts were selected and read by two reviewers, and the reference lists from those sources were then searched for additional trials.

Inclusion criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published English-language reports or published abstracts of:

1. RCTs comparing gemcitabine, either alone or in combination, with best supportive care or other therapy for cholangiocarcinoma or gallbladder cancer; and
2. Phase II trials reporting on the efficacy or adverse effects detected in treatment with gemcitabine, alone or in combination, in the treatment of cholangiocarcinoma or gallbladder cancer.

Exclusion criteria

Letters and editorials were not eligible.

Synthesizing the evidence

None of the trials obtained were RCTs; therefore, no pooling of outcome data was possible.

RESULTS

Literature search results

A total of 13 trial reports were obtained (5-17). None of the reports obtained were RCTs; all were single-arm phase II studies. The sample sizes of the studies were small, ranging from 11 to 45 patients. Ten reports were available in fully published form (5-7,9-14,17) and three reports were available as abstracts only (8,15,16). Seven of the trials reported hospitals, government agencies or clinical trials groups as the sole source of funding (5,7-10,13,14). Five reported pharmaceutical sponsorship: three by Eli Lilly Canada (6,12,16), one by Sanofi-Synthelabo (11) and one by both Eli Lilly Canada and Hoffman-La Roche (17). One trial did not report the source of funding (15).

Of the trials obtained, three described gemcitabine monotherapy (5-7) and 10 described gemcitabine in combination with other drugs (8-17). None of the trials delineated between patients with gallbladder cancer versus those with cholangiocarcinoma.

Gemcitabine monotherapy

Efficacy outcomes: Three single-arm, phase II trials investigating gemcitabine monotherapy were obtained (Table 1) (5-7). The doses used appear in Appendix 2. Response rates ranged from 30% in two trials (6,7) to 36% (5); however, none of the

TABLE 1
Treatment outcomes by study

Author (reference) (location), year	Regimen	Number of patients*	Response rate (%) (CR+PR)	Median courses delivered	Median follow-up (weeks)	Median survival (weeks)	One-year survival (%)
Monotherapy with gemcitabine							
Gallardo et al (5) (Chile), 2001	GEM	26 (25)	36 (0+9)	4.2	21.9	30.0	16
Kubicka et al (6) (Germany), 2001	GEM	23	30 (0+7)	3.75	NR	37.2	NR
Tsavaris et al (7) (Greece), 2004	GEM	30	30 (0+9)	14	NR	56	56.7
Combination therapy with gemcitabine							
Carraro et al (8) (Argentina), 2001	GEM+CIS	11 (10)	50 (3+2)	4.1 (mean)	5.2	45.2	NR
Kuhn et al (9) (Germany), 2002	GEM+DOC	43	9.3 (0+4)	NR	58.8	44	40
Alberts et al (10) (USA), 2005	GEM+5-FU/LV	42	9.5 (0+5)	4	80	38.8	14
André et al (11) (France), 2004	GEM+L-OHP	33	35.5 (0+11)	8	NR	61.6	57
		23	22 (1+4)	8	NR	30.4	30.8
Doval et al (12) (India), 2004	GEM+CIS	30	36.6 (4+7)	4.5	NR	20	18.6
Hsu et al (13) (Taiwan), 2004	GEM+5-FU/LV	30 (28) [29]	21.4 (0+6)	4	174.4	18.8	20
Kornek et al (14) (Austria), 2004	GEM+MMC	25	20 (0+5)	4	NR	26.8	23
Reyes-Vidal et al (15) (Chile), 2004	GEM+CIS	44 (42)	48 (4+16)	NR	NR	28	NR
Tan et al (16), 2004	GEM+CARBO	15 (13)	30.8 (1+3)	NR	NR	NR	NR
Knox et al (17) (Canada), 2005	GEM+CAPE	45	31 (2+12)	7	44	56	49

**(Evaluated response) and [evaluated toxicity]. 5-FU/LV 5-fluorouracil/leucovorin; CAPE Capecitabine; CARBO Carboplatin; CIS Cisplatin; CR Complete response; DOC Docetaxel; EV Evaluated; GEM Gemcitabine; L-OHP Oxaliplatin; MMC Mitomycin-c; NR Not reported; PR Partial response*

patients across those trials (n=78) experienced a complete response. Median survival rates reported ranged from a low of 30 weeks (5) to a high of 56 weeks (7). One-year survival rates ranged from 16% (5) to 57% (7).

Adverse effects: Adverse effects observed in the trials of gemcitabine monotherapy are described as follows: one trial (5) reported no grade 3/grade 4 adverse effects and one trial (7) reported no grade 4 adverse effects. Two trials reported either grade 3 or grade 4 neutropenia (6,7). At least one trial reported the following grade 3/grade 4 effects: anemia (6); nausea (6); flu-like symptoms (6); hemolytic uremic syndrome (6); and anorexia (7). Generally, the gemcitabine monotherapy trials reported that any adverse effects observed were mild and manageable. See Appendix 3 for adverse effects tables.

Quality of life: None of the trials on gemcitabine monotherapy reported data on quality of life.

Gemcitabine in combination with other drugs

Efficacy outcomes: Ten single-arm, phase II trials investigating gemcitabine in combination with other drugs were obtained (Table 1) (8-17). Gemcitabine was tested in combination with cisplatin (8,12,15), docetaxel (9), 5-fluorouracil (5-FU) and leucovorin (10,13), oxaliplatin (11), mitomycin-c (14), carboplatin (16) and capecitabine (17). The doses used are shown in Appendix 2.

Response rates ranged from lows of 9.3% with gemcitabine plus docetaxel (9) to highs of 50% (8), 37% (12) and 48% (15) with gemcitabine in combination with cisplatin. Only patients receiving gemcitabine in combination with cisplatin (8,12,15), oxaliplatin (11), carboplatin (16) or capecitabine (17) demonstrated complete responses (11 of 85 [13%] for gemcitabine with cisplatin, one of 22 [5%] with oxaliplatin, one of 13 [8%] with carboplatin and two of 45 [4%] with capecitabine).

Adverse effects: A variety of grade 3/grade 4 adverse effects were observed in the trials of gemcitabine in combination with other drugs. The three trials investigating gemcitabine in combination with cisplatin (8,12,15) reported granulocytopenia (8), thrombocytopenia (8,12,15), fever (8), asthenia (8), anorexia (8), neutropenia (12,15), anemia (12,15) and leukopenia (15). The trial investigating gemcitabine in combination with docetaxel (9) reported alopecia, nausea and vomiting, mucositis, leukopenia, thrombocytopenia and anemia. The trial investigating gemcitabine in combination with 5-FU and leucovorin (10,13) reported dyspnea, nausea and vomiting, fatigue, thrombocytopenia, diarrhea, infection, leukopenia, anemia and elevation of liver enzymes. The trial investigating gemcitabine in combination with oxaliplatin (11) reported neutropenia, thrombocytopenia, nausea and vomiting, and peripheral neuropathy. The trial investigating gemcitabine in combination with mitomycin-c reported leukopenia and thrombocytopenia. The trial investigating gemcitabine in combination with carboplatin (16) reported nausea and vomiting, elevation of liver enzymes, proteinuria, hematuria, edema and fatigue. The trial investigating gemcitabine in combination with capecitabine (17) reported neutropenia (one patient with febrile neutropenia), thrombocytopenia, hand-foot rash, infection, fatigue and thromboembolitis. See Appendix 3 for adverse effects tables.

Quality of life: None of the trials on gemcitabine combination therapy reported data on quality of life.

DISCUSSION

The most effective treatment for cancer of the gallbladder is surgical resection of the primary tumour along with any local spread (1), but surgery is dependent on the patient presenting at an early, resectable stage. Curative resection of cholangiocarcinoma is more complex and is dependent on the site and extent of the tumour (1). Five-year survival after the surgical resection of stage I gallbladder cancer should be greater than 85% (1), but drops to 25%, 10% and 2% for stage II, III and IV tumours, respectively (1). For patients with resectable cholangiocarcinoma, five-year survival rates range from 35% to 45% (1). There

is no generally accepted standard chemotherapy for advanced, nonresectable cancer of the gallbladder or biliary tree. In advanced disease, median survival with best supportive care is approximately six months, and five-year survival rates approach 0% (1). In past phase II studies, response rates for the use of fluoropyrimidines in this population ranged from 10% to 24% (1).

Gemcitabine, either alone or in combination with other commonly used drugs such as fluoropyrimidines (10,13,17) or cisplatin, (8,12,15) has shown positive activity and response in phase II trials for the treatment of advanced biliary cancer. Single studies of gemcitabine in combination with oxaliplatin (11) and carboplatin (16) also suggest a similar response.

Considering the low incidence rate of these types of tumours and the poor performance status of many patients presenting with biliary cancer, conducting large trials to establish a standard of care is unlikely. Indeed, a search of the National Cancer Institute's Internet Clinical Trials Database (http://www.cancer.gov/search/clinical_trials/) on March 23, 2005, for reports of new or ongoing trials revealed only two small phase II trials (SWOG-S0202 and NCI-6254). Information on a third phase II trial (SAKK-44/02) was submitted by an Ontario clinician. Therefore, treatment decisions must be based on the balance of predictable toxicities and benefits. While none of the studies included in this systematic review measured and evaluated quality of life scores, the assumption that some benefit may accrue from complete and partial responses, if not also from stabilization of the disease, seems reasonable. Certainly the extension of median survival to over one year in some studies exceeds best supportive care by as much as six months.

Therefore, administering a trial of gemcitabine in selected patients, either as a single agent or in combination with other drugs that have demonstrated a response in this treatment population, seems reasonable. In general, fluoropyrimidines have a more favourable toxicity profile than the alkylating platinum compounds (cisplatin, oxaliplatin and carboplatin). Considering the improved response rates and survival in combination therapy, the use of gemcitabine and a fluoropyrimidine appears to be favoured. Knox et al (17), in their most recent article, stated that a previous retrospective review of gemcitabine and continuous infusion 5-FU (18) showed a similar benefit in terms of response but with increased line-related infections and thromboembolitic complications, which suggests that when gemcitabine is given with a fluoropyrimidine, the fluoropyrimidine of choice should be capecitabine.

CONCLUSIONS

Recommendations

See Appendix 2 for recommended regimens and doses.

- In appropriate patients with gallbladder cancer or cholangiocarcinoma, surgical resection offers the best chance for survival and should be the first treatment of choice.
- For patients who are not considered candidates for surgery with curative intent but who are willing and able to tolerate treatment with the chemotherapy, gemcitabine, either alone or in combination with a fluoropyrimidine (such as 5-FU or capecitabine), appears to be a reasonable alternative to best supportive care, although this conclusion has not been confirmed with an RCT.
- Patients should be encouraged to enroll in RCTs comparing promising new treatments, such as gemcitabine in combination with a fluoropyrimidine, against other treatments with proven response.

Future research

Patients with cancers of the biliary tree should be encouraged to enroll in clinical trials designed to assess the efficacy, adverse effects and quality of life scores of gemcitabine, either alone or in combination, compared with other treatments with proven response.

Related clinical practice guidelines: The PEBC Practice Guideline Report #2-10: *Use of gemcitabine in the treatment of advanced pancreatic carcinoma.*

CONFLICTS OF INTEREST: The authors declared no conflicts of interest related to the topic of this report.

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APPENDIX 1

Cancer Care Ontario's Program in Evidence-Based Care's Gastrointestinal Cancer Disease Site Group

Dr Jean Maroun (Co-chair), Dr Bernard Cummings (Co-chair), Dr Olusegun Agboola, Mr Murray Citron (Patient Representative), Dr Scott Berry, Dr James J Biagi, Dr Franco Denardi, Dr Sheldon Fine, Dr Barbara Fisher, Dr Derek Jonker, Dr Juhu Kamra, Dr Walter Kocha, Ms Marion Lethbridge (Patient Representative), Dr Richard Malthaner, Dr Malcolm Moore, Dr Marko Simunovic, Dr Andy Smith, Dr Ved Tandan and Dr Rebecca Wong. Please see the Cancer Care Ontario's Program in Evidence-Based Care's Web site at <www.cancercare.on.ca/index_gastrointestingalCancerDSG.htm> for a complete list of current and past Gastrointestinal Cancer Disease Site Group members.

APPENDIX 2
Dosing by trial

Monotherapy regimens	
Gallardo et al (5), 2001	1000 mg/m^2 gemcitabine IV for 30 min/week, three weeks of every four weeks
Kubicka et al (6), 2001	1000 mg/m^2 gemcitabine IV for 30 min/week, three weeks of every four weeks
Tsavaris et al (7), 2004	800 mg/m^2 gemcitabine IV for 30 min/week, without cessation, until severe toxicity, disease progression or patient refusal arose

Continued on next page

APPENDIX 2 – continued

Combination therapy regimens

Carraro et al (8), 2001	1000 mg/m^2 gemcitabine as a 30 min infusion, followed by 30 mg/m^2 cisplatin IV bolus injection, administered on days 1, 8 and 15 of each cycle, repeated every 28 days
Kuhn et al (9), 2002	1000 mg/m^2 gemcitabine, followed by 35 mg/m^2 docetaxel once a week, for three weeks, followed by one week of rest
Alberts et al (10), 2005	1000 mg/m^2 gemcitabine IV for 30 min, followed by 25 mg/m^2 leucovorin calcium IV push, followed immediately by 600 mg/m^2 5-FU IV push on days 1, 8 and 15, repeated every four weeks
André et al (11), 2004	1000 mg/m^2 gemcitabine as a 10 mg/m^2/min infusion on day 1, followed by a 2 h infusion of 100 mg/m^2 oxaliplatin on day 2, every two weeks
Doval et al (12), 2004	1000 mg/m^2 gemcitabine 30 min to 60 min infusion and 70 mg/m^2 cisplatin 2 h infusion were given on day 1, 1000 mg/m^2 gemcitabine alone was given on day 8, in a 21 day cycle
Hsu et al (13), 2004	800 mg/m^2 gemcitabine IV infusion for 30 min followed by 2000 mg/m^2 5-FU and 3000 mg/m^2 leucovorin IV for 24 h on days 1, 8 and 15, repeated every four weeks
Kornek et al (14), 2004	2000 mg/m^2 gemcitabine on days 1 and 15, with 8 mg/m^2 MMC on day 1 only, repeated every four weeks
Reyes-Vidal et al (15), 2004	1250 mg/m^2 gemcitabine and 35 mg/m^2 cisplatin on days 1 and 8, every 21 days, for a total of six cycles
Tan et al (16), 2004	1000 mg/m^2 gemcitabine IV over 30 min on days 1 and 8, with carboplatin at area under the curve 5 IV on day 1 only, of a 21 day cycle
Knox et al (17), 2005	1000 mg/m^2 gemcitabine IV over 30 min on days 1 and 8, with 650 mg/m^2 capecitabine orally twice a day for 14 days, three-week cycle; treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent

5-FU 5-fluorouracil; IV Intravenously; MMC Mitomycin-c

APPENDIX 3
Adverse effects

Gemcitabine monotherapy

Trial	Neutropenia (pts)	Anemia (pts)	Nausea (pts)	Flu-like (pts)	Hemolytic uremic syndrome (pts)	Anorexia (pts)
Gallardo et al (5), 2001 (WHO scale)	*No gastrointestinal toxicity or grade 3/grade 4 hematological episodes were recorded*					
Kubicka et al (6), 2001	13% (1)	4% (1)	13% (3)	4% (1)	4% (1)	NR
Tsavaris et al (7), 2004 (WHO scale)	3.3% (1)	NR	NR	NR	NR	3.3% (1)
	No grade 4 adverse effects were observed					

Gemcitabine in combination with cisplatin

Trial	Neutropenia (pts)	Anemia (pts)	Fever (pts)	Asthenia (pts)	Anorexia (pts)	Granulocytopenia (pts)	Thrombocytopenia (pts)	Leukopenia (pts)
Carraro et al (8), 2001 (NCIC-CTC scale) Grade 3 only	0%	NR	9% (1)	9% (1)	9% (1)	9% (1)	18% (2)	NR
	Two pts died during treatment; one from cerebral ischemia after cycle one and one from an undetermined cause							
Doval et al (12), 2004 (WHO scale) Grade 3/grade 4 only	33.2% (10)	36.6% (11)	NR	NR	NR	NR	16.6% (5)	NR
Reyes-Vidal et al (15), 2004 (WHO scale)	23%	14%	NR	NR	NR	NR	2%	7%
	Two pts died following the first course of treatment, one due to renal toxicity and one due to disease progression							
	No WHO grade 4 adverse events were reported							

Gemcitabine in combination with docetaxel

Trial	Alopecia (pts)	Nausea and vomiting (pts)	Mucositis (pts)	Leukopenia (pts)	Thrombocytopenia (pts)	Anemia (pts)
Kuhn et al (9), 2002 (WHO scale) Grades 3 and 4	65.1% (28)	18.6% (8)	4.6% (2)	9.3% (4) Grade 3 only	2.3% (1) Grade 3 only	2.3% (1) Grade 3 only

Gemcitabine in combination with 5-FU/folinic acid

Trial	Dyspnea (pts)	Nausea and vomiting (pts)	Fatigue (pts)	Thrombocyto-penia (pts)	Diarrhea (pts)	Infection (pts)	Leukopenia (pts)	Anemia (pts)	Increased liver enzymes (pts)
Alberts et al (10), 2004 Grades 3 and 4	(4)	(8)	(7)	(6)	(4)	NR	NR	NR	NR
Hsu et al (13), 2004 (WHO scale) Grades 3 and 4	NR	7% (2)	NR	10% (3)	NR	31% (9)	14% (4)	10% (3)	10% (3)

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APPENDIX 3 – continued

Gemcitabine in combination with oxaliplatin

Trial	Neutropenia (pts)	Thrombocytopenia (pts)	Nausea and vomiting (pts)	Peripheral neuropathy (pts)
Andre et al (11), 2004 (NCIC-CTC scale) Grades 3 and 4	14%	9%	5%	7%

Gemcitabine in combination with mitomycin-c

Trial	Leukopenia (pts)	Thrombocytopenia (pts)
Kornek et al (14), 2004 (WHO scale) Grades 3 and 4	17% (4)	13% (3)

Gemcitabine in combination with carboplatin

Trial	Nausea and vomiting (pts)	Increase in liver enzymes (pts)	Proteinuria (pts)	Hematuria (pts)	Edema (pts)	Fatigue (pts)
Tan et al (16), 2004	*No grade 4 toxicities were reported. Grade 3 hematological toxicities were rare (three ANC, one platelet) Nonhematological toxicities were considered mild and included nausea, vomiting, elevated LFTs, proteinuria, edema and fatigue*					

Gemcitabine in combination with capecitabine

Trial	Neutropenia (pts)	Thrombocytopenia (pts)	Hand-foot rash (pts)	Infection (pts)	Fatigue (pts)	Thromboembolitic (pts)
Knox et al (17), 2005 (NCIC-CTC scale) Grades 3 and 4	34% (15)	11% (5)	9% (4)	4% (2)	4% (2)	2% (1)

5-FU 5-fluorouracil; ANC Absoluted neutrophil count; LFT Liver function test; NCIC-CTC National Cancer Institute of Canada's Common Toxicity Criteria; NR Not reported; Pts Patients; WHO World Health Organization

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